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microspheres are then applied to the sensor. The sensor detects the presence of NO by a decrease in fluorescence of the dye. The fluorescence of the dye is compared to the fluorescence of the microspheres, which is relatively insensitive to NO (see p. 4904, second column, second full paragraph).

In contrast, claim 1 is directed to a substrate with a surface comprising discrete sites, wherein a reflective coating is on the surface. Furthermore, a population of microspheres comprising at least first and second subpopulations are distributed on the substrate. Claim 29 is directed to a composition that includes a substrate with a surface comprising discrete sites and a population of microspheres distributed on the substrate, wherein the microspheres include a bioactive agent and a signal transducer element.

As the Examiner is aware, “[i]t is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention.” *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). The law is well established that in order to anticipate a claim, the prior art must disclose “each and every element” of the claimed invention.

In the present case, Applicants respectfully submit that Barker fails to teach each and every element of the claims. That is, as noted above, the sensor of Barker includes a dye immobilized to a gold surface and reference microspheres deposited on the sensor. However, Barker does not teach a first and second subpopulation of microspheres distributed on the substrate. Accordingly, Applicants submit that Barker fails to anticipate claim 1.

In addition, Applicants note that the microspheres of Barker do not include a bioactive agent and signal transducer agent. In contrast, the microspheres of Barker are fluorescent reference microspheres. In Barker, the bioactive agent of the sensor is not on the microspheres; rather it is attached to the gold that is assembled on the substrate. Accordingly, Applicants

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respectfully submit that Barker fails to anticipate the claimed invention. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 17-23 are rejected under 35 U.S.C. § 102(e) as being anticipated by Walt et al. (6,023,540). Applicants respectfully traverse.

Walt describes a microsphere based sensor that includes microspheres randomly distributed in wells on the surface of a substrate. The microspheres of Walt include different functionalities as well as an optical encoding scheme. However, Walt is silent with respect to teaching alternatively shaped wells as presently claimed.

Applicants note that claim 17 has been amended to depend from claim 1. Thus, claims 17-23 now depend from claim 1 which recites that a reflective coating is on the surface of the substrate. Applicants submit that Walt is silent with respect to a reflective coating on the substrate. As such, Walt does not anticipate claims 17-23, as amended.

In addition, Applicants note that claim 47 has been added, which is similar to previously pending claim 21 written in independent form, and recites that the geometrically shaped well has a cross section selected from the group consisting of a square, a star, a triangle, a pentagon and an octagon. Applicants submit that Walt is silent with respect to such alternative shapes. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

35 U.S.C. § 103

Claim 24 is rejected under 35 U.S.C. § 103 as being obvious over Walt (6,023,540) in view of Barker et al. (Analytical Chemistry, (1998) 70:4902-4906).

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Walt and Baker are described above. Basically, the Examiner suggests that it would have been obvious for one of skill in the art “to combine and substitute a composition, wherein the substrate is a transparent substrate comprising a first and a second surface, the first surface comprising discrete sites, and a reflective coating on the second surface of Barker et al. into the composition of Walt et al.” (see p. 7 of the Office Action). Applicants respectfully traverse.

As the Examiner is aware, to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant’s disclosure. In re Vaeck, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Initially, Applicants would like to clarify the teachings of Barker. The Examiner suggests that Barker teaches a composition wherein the substrate comprises a first and a second surface, wherein the first surface comprises discrete sites, the reflective coating on the second surface and a population of microspheres distributed on the first surface (citing the Abstract and Experimental section, Sensor Preparation Subsection). However, Applicants submit that nowhere in Barker is there such teaching of a substrate with a first and a second surface which

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has the reflective coating on the second surface and discrete sites with microspheres on the first surface.

In contrast, the sensor in Barker includes a substrate which has gold applied to it, dyes applied to the gold and reference microspheres distributed on the gold. That is, the gold, dyes and microspheres are applied to the same surface of the substrate. Applicants fail to see where the gold and microspheres are applied to different sides of the substrate. As noted by the Examiner, Walt also is silent with respect to teaching a transparent substrate with a reflective coating on one surface and discrete sites on the other. As such, Applicants submit that the prior art references when combined do not teach all of the claim elements and a *prima facie* case of obviousness has not been established.

In addition, Applicants submit that the Examiner has failed to provide adequate motivation for the combination of the references. The Examiner suggests that the skilled artisan would have been motivated to combine the references because Barker et al. state “[t]he new fluorescein derivative chemical sensors have characteristics similar to those of the protein-based biosensors, including fast response times, excellent selectivity, and complete reversibility. In addition, the chemical sensors have advantages such as greater stability and commercially available components”. However, Applicants submit that this is a legally incorrect determination of motivation. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Here, there is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention.

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In addition, the Examiner's attention is respectfully drawn to *In re Lee*, 61 USPQ2d 1430 (CA FC 2002). In this case, the Examiner rejected the claims under 35 U.S.C. §103 and stated that the required motivation "would be that the automatic demonstration mode is user friendly and it functions as a tutorial". *Id.* at 1435. The Federal Circuit stated that "deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is "basic knowledge" or "common sense". The Board's finding must extend to all material facts and must be documented on the record, lest the "haze of so-called expertise" acquire insulation from accountability. "Common knowledge" and "common sense", even if assumed to derived from the agency's expertise, do not substitute for authority when the law requires authority." (citing *In re Zurko*, 59 USPQ2d 1693 (CA FC 2001); see *Lee*, 1434-1435). In the present case Applicants submit that the Examiner has failed to point to anything specific in the cited references that would suggest or provide the motivation to combine the references or to modify them. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under *In re Lee*.

In this case, the Examiner has essentially used impermissible hindsight and "common sense" to conclude that the combination of these two references would have been motivated by the ordinary artisan employing "scientific reasoning" to combine the teachings of the two references. This is legally incorrect under the Federal Circuit's analysis. Moreover, as noted above, even when combined, the references do not teach the claimed invention.

Accordingly the rejection is improper and the Applicants respectfully request the Examiner to withdraw the rejection.

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Claim 9 is rejected under 35 U.S.C. § 103 as being obvious over Barker in view of Toriumi et al (5,896,227).

Barker is described above.

Toriumi et al describes a method for forming retroflective sheeting. The sheeting includes a binding layer and a retroflective element including microspheres. When microspheres include the retroflective coating it can be a dielectric coating.

Basically the Examiner suggests that since Barker teaches the elements of claims 1-8 and 29-31 but does not teach that the reflective coating is a dielectric coating, it would have been obvious to substitute the dielectric coating of Toruimi into the device of Barker. Applicants respectfully traverse.

Again Applicants remind the Examiner that to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Initially, Applicants note that claim 9 (when depending from claim 1) requires a substrate with a surface comprising discrete sites, a reflective coating, wherein the reflective coating is a dielectric coating, and a population of microspheres distributed on the substrate wherein the microspheres comprising at least a first and a second subpopulation. However, as noted above, Barker does not teach a first and second subpopulation of microspheres distributed on the substrate. Likewise, Toriumi fails to teach a first and second subpopulation of microspheres. Accordingly, not all claim elements are taught or suggested in the cited references.

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Applicants note also that claim 9 (when depending from claim 3) requires that the substrate include a first and a second surface, wherein the first surface comprises the discrete sites on which the microspheres are distributed and the reflective coating, which is a dielectric coating) is on the second surface. In contrast, Applicants submit that neither Barker nor Toriumi et al teach a substrate with a first and a second surface which has the reflective coating on the second surface and discrete sites with microspheres on the first surface. As such, Applicants submit that not all claim elements are taught or suggested in the prior art.

In addition, Applicants submit that there is insufficient motivation to combine the references. The Examiner poses different bases for motivation; however for the following reasons, Applicants submit that each of these fall short of the requisite level of motivation to combine references.

First, the Examiner suggests that it would have been obvious to one of ordinary skill in the art to combine and substitute a composition, wherein the reflective coating is a dielectric coating of Toriumi et al. into the method of Barker et al., since Toriumi et al state "Preferably the microspheres have a reflective coating on a portion thereof, e.g., a hemispheric coating of aluminum, silver or a dielectric coating. Such microspheres will be self-retroreflecting" (see p. 8 of the office action, citing column 7, lines 42-45). However, Applicants submit that such teaching would not suggest a combination of the references to reach the claimed invention. Applicants note that the claims do not recite that the microspheres are reflective. Rather, the claims recite that the substrate has a reflective coating on the surface. Microspheres are then distributed on the surface. Applicants submit, therefore, that one of skill in the art would not have been motivated to combine Toriumi with Barker.

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The Examiner also suggests that one of skill in the art would be motivated based on employing scientific reasoning and in order to improve the synthesis of array of biomolecules. However, Applicants submit that this general assertion does not rise to the level required to motivate one of skill in the art to combine references. Applicants also note that the source of the motivation is unclear. That is, the Examiner has not documented the source of the motivation.

Again, Applicants look to In re Lee, 61 USPQ2d 1430 (CA FC 2002) (see above). The Federal Circuit stated that “deficiencies of the cited references cannot be remedied by the Board’s general conclusions about what is “basic knowledge” or “common sense”. The Board’s finding must extend to all material facts and must be documented on the record, lest the “haze of so-called expertise” acquire insulation from accountability. “Common knowledge” and “common sense”, even if assumed to derived from the agency’s expertise, do not substitute for authority when the law requires authority.” (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435). In the present case Applicants submit that the Examiner has failed to point to anything specific in the cited references that would suggest or provide the motivation to combine the references or to modify them. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under In re Lee.

Finally, Applicants note that the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Here, there is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention.



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Accordingly, Applicants submit that a prima facie case of obviousness has not been established. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 1-19, 24 and 29-31 are rejected under 35 U.S.C. § 103 as being obvious over Walt (6,023,540) in view of Toriumi et al (5,896,227).

Both references have been described above. Basically the Examiner's position seems to be that it would have been obvious for one of skill in the art "to combine and substitute a composition, wherein the reflective coating is a metal or dielectric coating of Toriumi et al. into the method of Walt et al." (p. 11 of the office action). Applicants respectfully traverse.

As has been noted, to establish a prima facie case of obviousness, three basic criteria must be met. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There must be a reasonable expectation of success, and the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Here Applicants submit that there is lacking any teaching or suggestion that would have motivated one of skill in the art to combine the references to reach the claimed invention. The Examiner suggests that the skilled artisan would have been motivated to combine the references because Toriumi et al state, "Preferably the microspheres have a reflective coating on a portion thereof, e.g., a hemispheric coating of aluminum, silver or a dielectric coating. Such microspheres will be self-retroreflecting (Column 7, lines 42-45)" (see p. 11 of the office action). However, again Applicants note that the claims as pending herein state that it is the substrate which has a reflective coating, not the microspheres. As such, Applicants submit that the skilled artisan would not have taken this teaching as motivation to combine Toriumi with Walt to reach the claimed invention.

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The Examiner also suggests that motivation resides in the teaching of Walt that “A microsphere-based analytic chemistry system is disclosed in which microspheres carrying different chemical functionalities may be mixed together while the ability is retained to identify the functionality on each bead using an optically interrogatable encoding scheme” (see p. 11 of the office action, citing Abstract, first sentence of Walt). However, Applicants submit that this general description of the system disclosed in Walt is not sufficient to motivate one of skill in the art to combine Walt with Toriumi. To this end, Applicants note that it is improper to cite to only general guidance as to the particular form of the claimed invention or how to achieve it. See In re O’Farrell, 853 F. 2d 894,903, 7 USPQ2d 1673,1681 (Fed. Cir. 1988).

In addition, Applicants submit that this is a legally incorrect determination of motivation. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Here, there is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention. That is, while Walt et al. describes the use of microspheres for the detecting a target, there is nothing cited to in either reference that would have motivated one of skill in the art to combine the array of Walt with the teachings of Toriumi.

Finally, the Examiner suggests that one of skill in the art, using “scientific reasoning” would have combined the references “in order to improve the synthesis of array of biomolecules”. However, Applicants submit that this is a legally incorrect determination of motivation. As noted previously, the Examiner has failed to point to any teaching to support this motivation, namely that the combination of references would result in improved synthesis of array of biomolecules. Applicants remind the Examiner of In re Lee as noted above. The

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Federal Circuit stated that “deficiencies of the cited references cannot be remedied by the Board’s general conclusions about what is “basic knowledge” or “common sense”. The Board’s finding must extend to all material facts and must be documented on the record, lest the “haze of so-called expertise” acquire insulation from accountability. “Common knowledge” and “common sense”, even if assumed to derived from the agency’s expertise, do not substitute for authority when the law requires authority.” (citing In re Zurko, 59 USPQ2d 1693 (CA FC 2001); see Lee, 1434-1435). In the present case Applicants submit that the Examiner has failed to point to anything specific in the cited references that would suggest or provide the motivation to combine the references or to modify them. The Examiner has also failed to document on the record what the common knowledge consists of by pointing to specifics and this is legally incorrect under In re Lee.

Accordingly, because a prima facie case of obviousness has not been established, Applicants respectfully submit that the rejection of claims based on 35 U.S.C. § 103 obviousness is improper. Applicants respectfully request the Examiner to withdraw the rejections.

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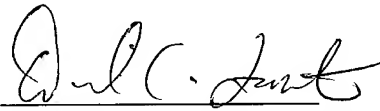
**CONCLUSION**

Applicants respectfully submit that the claims are in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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Appendix A  
Pending claims

1. A composition comprising:
  - a) a substrate with a surface comprising discrete sites;
  - b) a reflective coating on said surface; and
  - c) a population of microspheres distributed on said substrate said microspheres comprising at least a first and a second subpopulation.
2. A composition according to claim 1 wherein at least one subpopulation comprises a bioactive agent.
3. A composition according to claim 1, wherein said substrate comprises a first and a second surface, wherein said first surface comprises said discrete sites, said reflective coating on said second surface, said population of microspheres distributed on said first surface.
4. A composition according to claim 1 or claim 3, wherein said substrate is a fiber optic bundle.
5. A composition according to claim 4, wherein said fiber optic bundle comprises wells comprising said microspheres.
6. A composition according to claim 1 or claim 3, wherein said substrate is selected from the group consisting of glass and plastic.
7. A composition according to claim 1 or claim 3, wherein said reflective coating is a metal.
8. A composition according to claim 7, wherein said metal is selected from the group consisting of gold, silver, chromium, platinum and indium tin oxide.
9. A composition according to claim 1 or claim 3 wherein said reflective coating is a dielectric coating.
10. A composition according to claim 1 or claim 3, wherein said reflective coating selectively absorbs certain wavelengths.
17. (Amended) An array composition according to claim 1 or 3, wherein said discrete sites comprise alternatively shaped wells.

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18. A composition according to claim 17, wherein the wall angle of said alternatively shaped wells is a sloped wall angle.
19. A composition according to claim 17, wherein said alternatively shaped wells contain a rounded wall interior.
20. A composition according to claim 17, wherein at least one of said alternatively shaped wells is a geometrically shaped well.
21. A composition according to claim 20, wherein said geometrically shaped well has a cross section selected from the group consisting of a square, a hexagon, a star, a triangle, a pentagon and an octagon.
22. A composition according to claim 17, further comprising a population of microspheres distributed in said wells.
23. A composition according to claim 22, wherein said population comprises at least first and second subpopulations, each of said subpopulations comprising a bioactive agent.
24. A composition according to claim 17, wherein said substrate is a transparent substrate comprising a first and a second surface, said first surface comprising discrete sites, and a reflective coating on said second surface.
29. An array composition comprising:
  - a) a substrate with a surface comprising discrete sites; and
  - b) a population of microspheres distributed on said substrate, wherein said microspheres comprise:
    - i) a bioactive agent; and
    - ii) a signal transducer element.
30. A composition according to claim 29, wherein said signal transducer element is a nucleotide intercalator.
31. A composition according to claim 29, wherein said signal transducer element is a fluorophore.

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47. (New) An array composition comprising a substrate with a surface comprising discrete sites comprising alternatively shaped wells, wherein said wells have a cross section selected from the group consisting of a square, a star, a triangle, a pentagon and an octagon.

**VERSION SHOWING CHANGES**

17. (Amended) An array composition [comprising] according to claim 1 or 3, wherein said [a substrate with a surface comprising] discrete sites [comprising] comprise alternatively shaped wells.

47. (New) An array composition comprising a substrate with a surface comprising discrete sites comprising alternatively shaped wells, wherein said wells have a cross section selected from the group consisting of a square, a star, a triangle, a pentagon and an octagon.